REMARKS

Second Supplemental Information Disclosure Statement

A Second Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

Election/Restriction

The Examiner maintains that Claims 1-12, 18, 24, 25, 29, 30, 33-38, 44, 49, 54 and 55 are drawn to a nonelected invention because the claims encompass antisense. In support of the rejection, the Examiner directs Applicants' attention to Claim 5.

Applicants respectfully disagree. Claims 1-12, 18, 24, 25, 29, 30, 33-38, 44, 49, 54 and 55 are drawn to a method for producing a recombinant retroviral particle, said particle comprising an RNA sequence ***which encodes SDI-1***, or a functional analogue or a functional fragment of the RNA sequence ***which encodes a polypeptide with SDI-1 activity of inhibiting cell proliferation***, comprising stably transfecting an isolated producer cell with a retroviral vector comprising a DNA sequence which ***encodes SDI-1*** or a functional analogue or functional fragment which ***encodes a polypeptide with SDI-1 activity of inhibiting cell proliferation***, said producer cell additionally harboring at least one DNA construct coding for proteins required for said retroviral vector to be packaged. Antisense RNA ***cannot*** encode SDI-1 or a polypeptide with SDI-1 activity of inhibiting cell proliferation.

Applicants teach that a ***nucleic acid sequence that expresses SDI- 1 in a cell causes growth arrest of the cell (inhibition of cell proliferation)*** (specification, page 1, line 17 - page 2, line 18). In accordance with known biochemical principles, Applicants teach that:

> Antisense sequences are nucleic acids (either DNA or RNA) whose sequence is ***complementary to the sequence of a target mRNA molecule (or its corresponding gene)*** so that it is capable of hybridizing with binding to the mRNA molecule (or gene) and ***thereby impairing (i.e. attenuating or preventing) the transcription of the gene into mRNA or the translation of the mRNA into a gene product*** . . . Antisense SDI-1 DNA sequence may thus be used to inhibit the production of endogenous SDI-1 and thereby ***stimulate the proliferation of cells*** (specification, page 3, lines 14-20), emphasis added).

Original Claim 1 was directed to:

> A retroviral vector carrying a DNA sequence encoding SDI-1, a functional analogue, or a fragment thereof, or an antisense SDI-1 DNA sequence;

and original Claim 5 is directed to:

> A retroviral vector according to Claim 1 carrying a DNA sequence which is antisense to the SDI-1 gene.

On May 3, 1999, Applicants' Attorney elected to prosecute the invention of Group I (Claims 1-4, 8-11, 13-17, 19-23, 26-28, 31 and 32) in a telephone conversation with the Examiner, and the election was confirmed in the Amendment mailed to the U.S. Patent Office on November 24, 1999. Subsequently, Claims 1-12, 18, 24, 25, 29, 30, 33-38, 44, 49, 54 and 55 have been amended, and as amended, do not encompass antisense RNA because these claims comprise an RNA sequence which ***encodes*** SDI-1, or a functional analogue or a functional fragment of the RNA sequence which ***encodes*** a polypeptide with SDI-1 activity of ***inhibiting cell proliferation***. As pointed out in the specification as filed, antisense RNA ***cannot*** encode SDI-1 and ***cannot*** encode a polypeptide with SDI-1 activity capable of inhibiting cell activity; antisense RNA impairs SDI-1 activity, and consequently, is used to ***stimulate cell proliferation***.

Claims 1-12, 18, 24, 25, 29, 30, 33-38, 44, 49, 54 and 55 are drawn to the ***elected*** invention because the claims ***do not*** encompass antisense RNA. The elected claims have been searched and there is no need for an additional search. Applicants respectfully request withdrawal of the most recent restriction and re-entry of Claims 1-12, 24, 25, 33-38, 44, 49, 54 and 55.

Objection to Claim 14

The Examiner states that Claim 14 "should be changed from 'The producer cell of Claim 13' to - - The isolated producer cell of claim 13 - - to parallel the claim language in claim 13" (Office Action, page 3).

Claim 14 has been amended in accordance with the Examiner's suggestion, thereby obviating the objection.

Rejection of Claims 15, 16, 20-23, 27, 28, 31, 32, 41, 42, 46, 47, 51, 52 and 56-61 under 35 U.S.C. §112, first paragraph

Claims 15, 16, 20-23, 27, 28, 31, 32, 41, 42, 46, 47, 51, 52 and 56-61 are rejected under 35 U.S.C. §112, first paragraph because the specification, "does not reasonably provide enablement for using any mode of delivery as broadly claimed, using producer cells or capsules to treat disease, or using analogues or fragments of SDI-1 to treat disease" (Office Action, page 3).

The Examiner states that Claims 21, 26, 27, 32, 59 and 63 "encompass any route of administration" and that in Claim 31 "the metes and bounds of 'nearby' are unclear" (Office Action, page 4). The Examiner states that Crystal and Feldman "taught the combination of vector and mode of delivery for gene therapy required to target the desired tissue and provide adequate expression of a protein such that a desired effect was obtained was unpredictable" (Office Action, page 4). The Examiner further notes that "Nabel was not available to the public until Jan. 26, 1999" (Office Action, page 4).

Applicants respectfully disagree. The claims have been amended to methods of treating a tumor or restenosis comprising administering the capsules, retroviral particles or producer cells at the site of the tumor or the restenosis. The Examiner states that the specification is "enabling for a method of treating restenosis or cancer by contacting the site of restenosis or cancer with a retrovirus encoding SDI-1 resulting in a therapeutic effect.

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness having due regard for nature of the invention and the state of the art... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed (In re Wands, 1400 U.S.P.Q.2d 1400, 1404 (CAFC 1988)).

As pointed out in the previously filed Amendment, Applicants have provided sufficient guidance for carrying out the claimed invention to those of skill in the art. Applying a standard of reasonableness having due regard for nature of the invention and the state of the art, it is clear that those of skill in the art would not find the experimentation to practice Applicants' claimed invention undue. Applicants again direct the Examiner's attention to the teaching of Crystal that "human gene transfer is feasible, can evoke biologic responses that are relevant to human

disease, and can provide important insights into human biology" and that "[a]dverse events have been uncommon and have been related to the gene delivery strategies, not to the genetic material being transferred" (Crystal, abstract). However, Applicants use retroviral vectors to deliver the SDI-1 sequence. Price *et al.* demonstrate "the utility of retrovirus vectors for the introduction of genes into neural cell precursors" *in vivo* (Price *et al.*, page 160, column 1); and Miller *et al.* teach that retroviruses "will be useful for the treatment of humans" (Miller *et al.*, page 989, column 3).

The data of Nabel *et al.* was published in Yang, Z.Y., *et al., Nat Med., 1(10)*:1052-6 (Oct. 1995), a copy of which is being filed concurrently as Exhibit A. Thus, the teachings of Nabel *et al.* were available at the time of Applicant's invention. As the Examiner notes in a previous Office Action, Nabel teach that "administering a viral vector encoding SDI-1 to a restenosis patient by catheter or direct injection into a blood vessel at the site of the restenosis resulting in a decrease in the intimal hyperplasia in said blood vessel" (Office Action dated December 31, 2001, paper no. 18, page 4).

Clearly, Applicants have provided an enabling disclosure for treating a disease, such as cancer or restenosis, comprising administering retroviruses which encode, and thereby deliver, SDI-1 to the cells of an individual.

The Examiner states that the "only disclosed use for the capsules [of Claims 15, 16, 20-23, 41, 42, 46, 47, 51, 52, 56-61, 63 and 64] comprising producer cells are for therapy *in vivo*" and that the "specification does not provide adequate guidance to use producer cells or capsules comprising producer cells to treat disease" (Office Action, page 5). The Examiner further states that "[n]o teachings in the art provide guidance for one of skill to obtain therapeutic levels of secretion of retrovirus using producer cells or capsules *in vivo*" (Office Action, page 6). The Examiner maintains that Crystal and Feldman teach that "the parameters required to obtain a therapeutic effect using gene therapy was unpredictable" and that the "results of Nabel (US 5,863,904)" were not published until Jan. 29, 1999 and "could not be used by one of skill at the time of filing" (Office Action, pages 6-7).

Applicants respectfully disagree. As pointed out above, the data of Nabel *et al.* was published in Yang, Z.Y., *et al., Nat Med., 1(10)*:1052-6 (Oct. 1995), a copy of which is being filed concurrently as Exhibit A, and thus, the teachings of Nabel *et al.* were available at the time of Applicant's invention. Furthermore, Crystal teach that "human gene transfer is feasible, can

evoke biologic responses that are relevant to human disease, and can provide important insights into human biology" and that "[a]dverse events have been uncommon and have been related to the gene delivery strategies, not to the genetic material being transferred" (Crystal, abstract). However, Applicants use retroviral vectors to deliver the SDI-1 sequence, and Price *et al.* demonstrate "the utility of retrovirus vectors for the introduction of genes into neural cell precursors" *in vivo* (Price *et al.*, page 160, column 1); and Miller *et al.* teach that retroviruses "will be useful for the treatment of humans" (Miller *et al.*, page 989, column 3).

In addition, Applicants are filing concurrently herewith Gunzburg, W.H., *Curr Opin Mol Ther. 3(5)*:437-438 (Oct., 2001) as Exhibit B and PCT/EP96/02748 as Exhibit C as evidence that at the time of Applicants' invention it was known in the art that producer cells and capsules comprising producer cells could be used *in vivo* to treat disease. In Exhibit B, intra-cerebral inoculation of retrovirus producing packaging cells are described (Exhibit B, page 437, column 2), and in Exhibit C, encapsulated cells producing viral particles are described.

The Examiner states that Applicants "have not provided the amount of inhibition required for a fragment *in vitro* that indicates the fragment is capable of treating disease" (Office Action, page 7). The Examiner further states that Applicants "have not provided data indicating any fragment has the same function as full length SDI-1" and that "[w]ithout such guidance, it would require one of skill undue experimentation to determine any fragment or analogue of SDI-1 capable of treating disease *in vivo*" (Office Action, page 7).

Applicants respectfully disagree. The Examiner has provided no evidence to support the assertion that undue experimentation would be required from one of skill in the art to obtain functional fragments and analogues of SDI-1 for use in Applicants' claimed invention, and thus, has not established that Applicants' specification is not enabling for use of functional fragments and analogues of SDI-1.

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness having due regard for nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed (In re Wands, 1400 U.S.P.Q.2d 1400, 1404 (CAFC 1988)).

In the specification as filed, Applicants teach that:

> The SDI-1 polypeptide is 164 amino acids long, but deletion of the carboxy terminal portion of the SDI-1 molecule (amino acids 72-164) do not significantly affect the inhibitory effect of the polypeptide. The active domains of SDI-1 are therefore present within a peptide fragment containing amino acids 1 to 71. Active domains also comprises amino acids 42 to 47, 53 to 58 and 66 to 71. Deletion of amino acids 53 to 58 was found to result in the greatest loss of DNA synthesis inhibitory activity (50% of full length DNA). Deletions of amino acids 42 to 47 and 66 to 71 also resulted in a loss of inhibitory activity but to a much lesser extent. Deletion analysis have thus indicated that the critical region of SDI-1 polypeptide must lie between amino acids 42 to 71, and fine studies implicate that the region between amino acids 48 to 65 are critical for the negative growth effect of the gene (specification, page 8, line 22 to page 9, line 4).

Applicants then provide specific examples of functional SDI-1 fragments on page 9, lines 5-12 of the specification as filed. Applicants clearly teach that such fragments can be introduced into cells, "and their capacity to inhibit DNA synthesis can be monitored" (specification, page 9, lines 11-12). Applicants also teach that functional analogues of SDI-1 "can be identified by random mutation or site directed mutagenesis" and that "[r]andom mutation of target gene sequences to obtain mutant proteins having the desired characteristics have been described previously" (specification, page 9, lines 16-19). The level of the skilled person in this art is high. Undue experimentation would not be required for a person of skill in the art to prepare a fragment or analogue of SDI, a known protein, and assess whether such fragment or analogue inhibits DNA synthesis (a functional fragment or analogue).

The Examiner further states that "[i]t would require one of skill undue experimentation to determine whether a retrovirus encoding amino acids 1-71 and 42-58 of human SDI-1 using any route of administration as broadly claimed would have a therapeutic effect" (Office Action, page 8).

As pointed out above, Applicants' claimed invention has been amended to recite methods of treating a tumor or restenosis comprising administering the retroviral vectors, capsules, retroviral particles or producer cells at the site of the tumor or the restenosis. The Examiner states that the specification is "enabling for a method of treating restenosis or cancer by contacting the site of restenosis or cancer with a retrovirus encoding SDI-1 resulting in a therapeutic effect.

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 31, 32 and 63 under 35 U.S.C. §112, second paragraph

The Examiner states that "the site of the tumor" in Claim 31 lacks antecedent basis and that the claim should read "The method . . ." (Office Action, page 8).

Claim 31 has been amended to recite the method according to Claim 27 wherein the recombinant retroviral particle is administered as an injection into the living animal body, including a human, at the site of the tumor.

The Examiner states that the metes and bounds of injection "nearby" is indefinite in Claims 31 and 63 (Office Action, page 8).

Claims 31 and 63 have been amended to delete the term "nearby".

The Examiner states that "administering a producer cell line according to Claim 13" is indefinite in Claim 32 and should also read "the producer cell line . . . " (Office Action, pages 8-9).

Claim 32 has been amended in accordance with the Examiner's suggestion.

The Examiner states that "an encapsulated packaging cell line comprising encapsulated cells having a core containing packaging cells harboring . . ." is unclear in Claim 63.

Claim 63 has been amended to recite a method for the treatment of a tumor or restenosis comprising implanting a capsule having a core, wherein the core comprises packaging cells harbouring: a) a retroviral vector carrying a DNA sequence encoding SDI-1, a functional analogue, a fragment thereof or an antisense SDI-1 DNA sequence; and b) at least one DNA construct coding for the proteins required for said retroviral vector to be packaged and wherein a porous capsule wall surrounds said core, said porous capsule wall being permeable to retroviral particles produced by the packaging cells, into the living animal body, including a human, at the site of the tumor.

As amended, the claims particularly point out and distinctly claim the subject matter which Applicant regard as the invention.

Rejection of Claims 13, 14, 19, 26-28, 31, 32, 39, 40, 45, 48, 50 and 53 under 35 U.S.C. §103(a)

Claims 13, 14, 19, 26-28, 31, 32, 39, 40, 45, 48, 50 and 53 are rejected under 35 U.S.C. §103(a) as being unpatentable over Miller or Price in view of Nabel. In response to Applicants' arguments in the previously filed Amendment, the Examiner states that "[i]t is unclear how the

difference between DNA and RNA viruses indicates the combined teachings are not enabling or are missing an element of the claim" (Office Action, pages 10-11).

In the entire Nabel *et al.* patent, the use of retroviral vectors is referenced twice, and these references are limited to 4 lines (column 3, lines 10-11 and column 4, lines 60-61). In the first mention of retroviral vectors (column 3, lines 10-11) Nabel *et al.* is discussing the use of viral vector systems in general, not in the context of expressing SDI-1. However, immediately after this comment, Nabel *et al.* clearly states that: ***Suitable viral vectors which express p21 useful in accordance with the present invention include adenoviral vectors, Ad5-360 in combination with pAD-BgIII . . . . Preferably adenoviral vectors are used*** (Nabel *et al.*, column 3, lines 11-16). It is of importance to recognize that Nabel *et al.* do not state at this point that a suitable vector is a retroviral vector.

Applicants' point was that based on the known differences in the life cycles of DNA viruses and RNA viruses, one of skill in the art would not be motivated to combine the teachings of Nabel *et al.* with the teachings of Miller *et al.* or Price *et al.* to produce Applicants' claimed invention because one of skill would not expect that a ***stably transfected producer cell line comprising a retroviral genome which encodes the SDI-1*** could be produced. When including an SDI-1 gene into a retroviral vector, the SDI-1 gene is transcribed and translated into protein. However, SDI-1 is known to inhibit cell proliferation and DNA synthesis, and thus, prevent cell division. Accordingly, a person of skill in the art would not expect to get a stable population of retrovirus producing cells (***a stable population of daughter packaging cells***) by stable integration of a recombinant retroviral vector comprising the SDI-1 gene. Rather, a person of skill in the art would expect that after integration of the retroviral vector into the genome of the packaging cell, division of the cell would be inhibited by virtue of the expressed SDI-1 protein, and thus, ***stable daughter packaging cells*** which produce RNA-virus would not be generated. However, Applicants have shown that stable populations of recombinant retroviral particles producing cells stably transfected with a retroviral vector comprising SDI-1 are generated. Thus, one of skill in the art would likely not have been motivated to use retroviral vectors to express SDI-1, despite the second reference to retroviral vectors in the Nabel *et al.* patent.

The Examiner further states that Nakanishi *et al.* "taught stably transfecting numerous cells with a vector encoding p21 (another name for SDI-1) that survived and replicated for at least 72 hours" (Office Action, page 12).

Nakanishi *et al.* transfected truncated p21 constructs into cells to identify the active regions of the p21 gene. However, Nakanishi *et al.* do not provide an expectation that a stable population of retrovirus producing cells (***a stable population of daughter packaging cells***) would be generated by stable integration of a recombinant retroviral vector comprising the SDI-1 gene. Thus, even with the teaching of the Nakanishi *et al.* reference, a person of skill in the art would expect that after integration of the retroviral vector into the genome of the packaging cell, division of the cell would be inhibited by virtue of the expressed SDI-1 protein, and thus, ***stable daughter packaging cells*** which produce RNA-virus would not be generated.

Nevertheless, Claims 13, 14, 19, 26, 27, 31, 32, 39, 40, 45, 48, 50 and 53 have been amended to recite the use of a ProCon vector (specification, page 12, lines 26-27). In particular, the claims have been amended to recite a retroviral vector comprising a 5' LTR region of the structure U3-R-U5; one or more sequences selected from coding and noncoding sequences; and a 3' LTR region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence containing a regulatory element or a promoter, followed by the U5 and R region, characterized in that at least one of the coding sequences is a sequence encoding SDI-1, a functional analogue thereof, or a functional fragment thereof, said SDI-1 sequence encoding a polypeptide with SDI-1 activity of inhibiting cell proliferation and being under transcriptional control of said regulatory element or promoter.

The combined teaching of Miller *et al.* or Price *et al.* in view of Nabel *et al.* do not direct one of skill in the art to use a ProCon vector. The combined teaching of Miller *et al.* or Price *et al.* in view of Nabel *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,
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